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| (21) International Application Number: PCT/US86/00793 (22) International Filing Date: 15 April 1986 (15.04.86) (31) Priority Application Numbers: 723,844 848,690 (32) Priority Dates: 16 April 1985 (16.04.85) 8 April 1986 (08.04.86) (33) Priority Country: US (71) Applicant: NASTECH PHARMACEUTICAL COMPANY, INC. [US/US]; 800 Veterans Memorial Highway, Hauppauge, NY 11788 (US). (72) Inventor: WENIG, Jeffrey ; 9 Dickens Avenue, Dix Hills, NY 11746 (US). (74) Agents: BURKE, Henry, T. et al.; Wyatt, Gerber, Shoup, Scobey & Badie, 261 Madison Avenue, New York, NY 10016 (US). | | (81) Designated States: AT (European patent), AU, BE (European patent), BR, CF (OAPI patent), CG (OAPI patent), CH (European patent), CM (OAPI patent), DE (European patent), DK, FR (European patent), GA (OAPI patent), GB (European patent), HU, IT (European patent), JP, KR, LU (European patent), ML (OAPI patent), MR (OAPI patent), NL (European patent), NO, SE (European patent), SN (OAPI patent), TD (OAPI patent), TG (OAPI patent). Published <i>With international search report.</i> |
| (54) Title: NASAL COMPOSITIONS CONTAINING VITAMIN B ₁₂ (57) Abstract Compositions for nasal administration of a vitamin B ₁₂ to a human suffering a vitamin B ₁₂ deficiency. It is concerned also with such compositions in dosage unit form and with methods of administering such compositions. | | |

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NASAL COMPOSITIONS CONTAINING VITAMIN B₁₂
Related Application

This application is a continuation in part of copending application serial number 723,844 filed April 16, 1985.

BACKGROUND OF THE INVENTION

This invention is concerned with compositions for nasal administration of a vitamin B₁₂ to a human suffering a vitamin B₁₂ deficiency. It is concerned also with such compositions in dosage unit form and with methods of administering such compositions.

Cyanocobalamin is a vitamin B₁₂, and is one of the B₁₂ class of vitamins which includes vitamin B_{12a} (hydroxocobalamin), vitamin B_{12b} (aquacobalamin), vitamin B_{12c} (nitrilcobalamin), coenzyme B₁₂ (5'-deoxyadenosine cobalamine) and methyl B₁₂ (methyl cobalamine). Cyanocobalamin is the principal member of the class, and the most widely employed in medicine. This invention will be described as it relates to cyanocobalamin, but those skilled in the art will recognize that the invention is applicable to the class.

Vitamin B₁₂ is an essential compound for normal growth, hematopoiesis, production of all epithelial cells and maintenance of myelin throughout the nervous system. It was first isolated from liver concentrate by Rickes and his coworkers in 1948 and structurally elucidated by Hodgkin and her coworkers in the late 1950's. It is currently commercially available as a tablet and as an injectable.

Therapeutically, vitamin B₁₂ is employed in the treatment of a variety of B₁₂ deficiency afflictions, principally anemias such as pernicious and dipyllobothrium latum. Although the minimum daily requirement of vitamin B₁₂ is approximately 0.1 ug, the generally prescribed initial therapeutic dose is 100 to 1000 ug given intramuscularly. Maintenance therapy with vitamin B₁₂ is usually 100 ug intramuscularly, monthly and must be continued for life.

Since pernicious anemia is often a disease of later years when many sufferers have reduced muscle mass or are atrophic, repeated intramuscular injections of vitamin B₁₂ can be inconvenient, painful and often require doctor's visits. In some cases at least in the early stages, hospitalization is required. As a result, there is a need for a more convenient, less painful and less expensive method of administering vitamin B₁₂, particularly one that would not require hospitalization or repeated physician contacts.

Unfortunately, up to the present time no efficient method of administering B₁₂ which will achieve therapeutically useful blood levels of the vitamin except parenteral administration has been devised.

In 1953 and 1954 Monto et al in Am. J. Med. Sci., 223, 113 (1953) and Arch. of Int. Med. 93,219 (1954) described administration of B₁₂ by nasal inhalation and instillation. The vehicles for administration were aqueous isotonic sodium chloride solution and lactose powder. Although the results were reported as effective, safe and economical, the fact is that parenteral administration remains the only method regarded by the medical community as a safe, reliable and effective method for treating vitamin B₁₂ deficiencies in humans. No composition for nasal inhalation or instillation has become commercially

available for nasal administration to mammals. Neither have there been any further publications describing nasal inhalation or instillation of which applicant is aware.

The difficulty with nasal instillation by nasal dosage as the procedure is described in the cited articles is that most of the B₁₂ passes immediately into the throat. It is not in contact with the nasal mucosa for a sufficient period of time to permit useful and uniform absorption. Most of the B₁₂ so administered is, in fact wasted.

Compositions have now been discovered for the nasal administration of B₁₂ which can be kept in contact with the nasal mucose for an extended period of time. During the time the compositions are in such contact, the B₁₂ is uniformly absorbed from the compositions through the nasal mucose and is then uniformly distributed systemically. The use of the compositions, because of the efficiency with which the B₁₂ is absorbed allows the use much lesser amounts of B₁₂ than is normally present in parenteral B₁₂ compositions. Moreover, since the patient can self administer the B₁₂, the need for hospitalization or physician contacts is minimized and may even be eliminated.

THE INVENTION

This invention provides vitamin B₁₂ containing compositions specifically formulated for nasal administration which will, unlike aqueous isotonic sodium chloride compositions, remain in contact with the nasal mucose for a sufficiently long period of time to permit consistent, continuous and uniform absorption of therapeutically effective amounts of a vitamin B₁₂ through the nasal mucous membrane.

The invention, therefore comprises compositions containing a therapeutically effective amount of a vitamin B₁₂, such compositions being sufficiently viscous to maintain themselves in the nasal passages for a period of time which is long enough so that most of the B₁₂ is absorbed. The compositions are stable, easy to handle, and may be self administered by the patient.

More specifically the compositions of the invention are for nasal administration and contain a therapeutically effective amount of a vitamin B₁₂ in an isotonic aqueous buffer at a pH of from about 4 to 6. The compositions may be in the form of gels, lotions, ointments, creams and the like and will contain a sufficient amount of a thickening agent so that the viscosity is from about 2500 to 6500 cps, although more viscous compositions even up to 10,000 cps may be employed. The preferred compositions have a viscosity of 2500 to 5000 cps, since above that range they become more difficult to administer.

Due to the efficiency with which the B₁₂ is adsorbed from the compositions of this invention, a therapeutically effective amount of B₁₂ for nasal administration will normally be appreciably less than for other methods of administration. Typically the concentration of B₁₂ in a composition of the invention will be 0.05% to 1% by weight based on the total weight. In dosage unit forms the dosage will normally be from about 50 to 1000 micrograms.

The pH of the compositions of this invention is from about 4 to 6. At this pH, B₁₂ is stable so that the compositions have a shelf life which may be a year or more. Additionally, at this pH, irritation of the nasal mucosa is minimal. The pH is maintained with a physiologically acceptable buffer composition suitably an acetate, citrate, phosphate, phthalate, borate, or other buffer.

Acetate and citrate buffers are preferred for convenience and economy.

The isotonicity of the composition is accomplished using sodium chloride, or other pharmaceutically acceptable agent such as dextrose, boric acid, sodium tartrate or other inorganic or organic solute. Sodium chloride is preferred particularly for buffers containing sodium ions.

Viscosity of the compositions is maintained at the selected level using a therapeutically acceptable thickening agent. Methyl cellulose is preferred because it is easily and economically available and is easy to work with. Other suitable thickening agents include, for example, xanthan gum, carboxymethyl cellulose, hydroxypropyl cellulose, carbomer, and the like. The preferred concentration of the thickener will depend upon the agent selected. The important point is to use an amount which will achieve the selected viscosity.

Preferred compositions within the scope of this invention will contain a humectant to inhibit drying of the mucous membrane and to prevent irritation. Any of a variety of humectants can be employed including, for example sorbitol, propylene glycol or glycerol. As with the thickeners, the concentration will vary with the selected agent, although the presence or absence of these agents, or their concentration is not an essential feature of the invention.

An enhanced absorption of B₁₂ across the mucous membrane can be accomplished employing a surfactant. Typically useful surfactants for these therapeutic compositions include polyoxyethylene derivatives of fatty acid partial esters of sorbitol anhydrides such as Tween 80, Polyoxyl 40 Stearate, Polyoxyethylene 50 Stearate and Octoxynol. The usual concentration is from 1% to 10% based on the total weight.

A preservative is generally employed to increase the shelf life of the compositions. Benzyl alcohol is suitable, although a variety of preservatives including, for example, Parabens, thimerosal, chlorobutanol, or benzalkonium chloride may also be employed. A suitable concentration of the preservative will be from 0.02% to 2% based on the total weight, although there may be appreciable variation depending upon the agent selected.

The therapeutically effective compositions of this invention are prepared by mixing the ingredients following generally accepted procedures. For example the selected components may be simply mixed in a blender, or other standard machine to produce a concentrated mixture which is then adjusted to the final concentration and viscosity by the addition of water.

A typical composition of this invention contains the following components per 100 ml.

| | |
|---------------------------------|---------------|
| Benzyl alcohol, NF | 1.50ml |
| Sodium chloride, NSP | 0.82gm |
| Methyl cellulose, USP (400 cps) | 2.00gm |
| Acetic acid, NF | 0.10gm |
| Sodium acetate (anhyd, USP) | 0.27gm |
| Sorbitol soln., USP | 5.00ml |
| Cyanocobalamine, USP | 0.10gm |
| Water, purified | q.s. 100.00ml |

The viscosity of the formulation is about 4500 cps. The pH is about 5.

The following non-limiting examples are given by way of illustration only and are not to be considered limitations of this invention of which many apparent variations are possible without departing from the spirit or scope thereof.

EXAMPLE 1

The following compositions prepared by mixing.

A

| | |
|--------------------------------|----------------|
| Phenylmercuric Acetate NF | 0.002g |
| Boric Acid NF | 1.740g |
| Methylcellulose (4000 CPS) USP | 2.000g |
| Acetic Acid NF | 0.100g |
| Sodium Acetate (Anhydrous) USP | 0.270g |
| Glycerin USP | 5.000ml |
| Cyanocobalamin USP | 0.100g |
| Water, Purified USP | q.s. 100.000ml |

B

| | |
|--|----------------|
| Benzalkonium Chloride NF | 0.020g |
| Potassium Chloride USP | 1.080g |
| Hydroxyethyl Cellulose (3500-4000 CPS) NF | 1.000g |
| Acetic Acid NF | 0.100g |
| Sodium Acetate (Anhydrous) USP | 0.270g |
| Propylene Glycol USP | 5.000ml |
| Cyanocobalamin USP | 1.000g |
| Water, Purified USP | q.s. 100.000ml |

C

| | |
|--------------------------------|---------|
| Thimerosal USP | 0.002g |
| Dextrose USP | 5.120g |
| Polysorbate 80 USP | 10.000g |
| Methylcellulose (4000 CPS) USP | 1.33g |
| Acetic Acid NF | 0.100g |
| Sodium Acetate (Anhydrous) USP | 0.270g |

| | | |
|--------------------|------|-----------|
| Glycerin USP | 8 | 5.000ml |
| Cyanocobalamin USP | | 0.500ml |
| Water, Purified | q.s. | 100.000ml |

D

| | |
|--------------------------------|----------------|
| Methylparaben NF | 0.020g |
| Propylparaben NF | 0.010g |
| Sodium Chloride USP | 0.820g |
| Xanthan Gum NF | 2.000g |
| Acetic Acid NF | 0.100g |
| Sodium Acetate (Anhydrous) USP | 0.270g |
| Propylene Glycol USP | 5.000g |
| Cyanocobalamin USP | 0.200g |
| Water, Purified | q.s. 100.000ml |

The viscosities of the compositions are within the range defined above.

This typical composition disclosed above just prior to the examples tested in humans in order to determine quantitative increases in B₁₂ Blood Levels following nasal administration. Three normal volunteers received 0.1cc of the cited composition (100ug B₁₂) inserted nasally with a nasal syringe applicator. Serial Blood Samples were drawn from the subjects at 0, 0.05, 0.08, 0.16, 0.25, 0.5, 1.0, 2.0, 3.0, 4.0, 6.0, 8.0, and 24 hours following dosing and assayed for B₁₂ content by radioimmunoassay.

It was found that in less than 15 minutes after administration the serum level of B₁₂ was significantly elevated and that significantly elevated blood levels were maintained during the full 24 hours of the study period.

The actual plasma blood levels of B₁₂, in the subjects following its nasal administration in the above cited composition, were:

| <u>TIME (hours)</u> | <u>PLASMA LEVELS (Picograms)</u> |
|---------------------|----------------------------------|
| 0 | 599 |
| 0.05 | 631 |
| 0.08 | 628 |
| 0.16 | 674 |
| 0.25 | 754 |
| 0.5 | 729 |
| 1.0 | 804 |
| 2.0 | 794 |
| 3.0 | 769 |
| 4.0 | 727 |
| 6.0 | 752 |
| 8.0 | 803 |
| 24.0 | 729 |

An additional and similar study was performed with three human subjects using the same composition in which 0.2cc was administered intranasally (200ug B₁₂). The actual plasma blood levels obtained were:

| <u>TIME (hours)</u> | <u>PLASMA LEVELS (Picograms)</u> |
|---------------------|----------------------------------|
| 0.0 | 591 |
| 0.05 | 630 |
| 0.08 | 637 |
| 0.16 | 680 |
| 0.25 | 699 |
| 0.5 | 742 |
| 1.0 | 809 |
| 2.0 | 849 |

| | |
|------|-----|
| 3.0 | 786 |
| 4.0 | 764 |
| 6.0 | 722 |
| 8.0 | 742 |
| 24.0 | 675 |

EXAMPLE 2

A composition of this invention containing the following components per 100 ml was prepared.

| <u>TIME (hours)</u> | <u>PLASMA LEVELS (Picograms)</u> |
|---------------------|----------------------------------|
| 0.0 | 731 |
| 0.05 | 734 |
| 0.08 | 725 |
| 0.16 | 845 |
| 0.25 | 837 |
| 0.5 | 940 |
| 1.0 | 975 |
| 2.0 | 1027 |
| 3.0 | 1038 |
| 4.0 | 1002 |
| 6.0 | 969 |
| 8.0 | 945 |
| 24.0 | 925 |

Again it was found that in approximately 15 minutes after administration the serum level of B₁₂ was significantly elevated and that significantly elevated blood levels were maintained during the full 24 hours of the study period.

EXAMPLE 3

The following comparative experiment was conducted on forty normal, human, adult volunteers to compare the availability, speed of availability, and duration of availability of B₁₂ administered by various routes. Commercially available oral and bilingual tablets were compared with the compositions of this invention which were administered orally. All samples were tested by high performance liquid chromatography for B₁₂ per dosage unit was as follows:

| | |
|---------------------------|-------|
| Methyl Cellulose | 20gm |
| Sodium Citrate | 3.2gm |
| Citric Acid | 1.2gm |
| Bengulkonium chloride 50% | 0.4ml |
| Cyanocolalamine | 2.5gm |
| Purified Water q.s. to | 100ml |

The composition used to prepare the 400 mcg intrumural dosage unit was identical except that it contained 4.0 gm. of cyanocolalamine.

Serial blood samples were from the subjects at 0, 5, 1, 2, 4, 8, 24, 48 and 72 hours following dosing and assayed for B₁₂ content by radioimmunoassay.

The results are shown in Figures 1, 2, 3 and 4 in which concentration in picograms per ml. is plotted against time. The results are also summarized in table 1. In the table, the Baseline is the B₁₂ average concentration of B₁₂ in the volunteer group prior to B₁₂ administration.

From an analysis of the figures and the tables, the following unexpected advantages for nasal administration of B₁₂ in the compositions of this invention will be apparent:

1. Increased blood levels at lower dosages.
2. Maximum blood levels achieved more rapidly, and at lower dosage levels.
3. High blood levels maintained for entire period of test as indicated by larger areas under the curve.
4. Substantially higher blood levels at lower dosages even two days after administration.

TABLE 1

A COMPARISON OF THE BIOAVAILABILITY OF VITAMIN B₁₂ FOLLOWING INTRANASAL,
ORAL, AND SUBLINGUAL ADMINISTRATION IN NORMAL SUBJECTS

| <u>Number of Subjects</u> | <u>Vitamin B₁₂ Treatment</u> | <u>Average Baseline pc/ml</u> | <u>Average Maximum Increase in Plasma B₁₂ Concentration</u> | <u>Average time to Reach Maximum B₁₂ Plasma Concentration</u> | <u>Average Area Under The Curve (pcg hr/ml)</u> | <u>Average Increase In Plasma B₁₂ Concentration in 48 hrs. (pcg/ml)</u> |
|-------------------------------|---|-----------------------------------|--|--|---|--|
| 10 | 500mcg Oral Tablet | 665.8 | 233.51 pcg/ml | 25.60 Hours | 9,503 | 92.6 |
| 10 | 500 mcg Sublingual Tablet | 599.8 | 196.64 pcg/ml | 5.70 Hours | 6,010 | 51.1 |
| 10 | 250mcg Intranasal | 577.2 | 1167.31 pcg/ml | 2.5 Hours | 24,266 | 193.5 |
| 10 | 400mcg | 472.1 | 1967.98 pcg/ml | 1.61 Hours* | 28,690 | 178.9 |

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* A 24:00 hour data point was considered and outlier and eliminated from the calculation of the average.

WHAT IS CLAIMED IS:

1. A therapeutic composition for nasal administration comprising a therapeutically effective amount of a vitamin B₁₂ in an isotonic aqueous buffer at a pH of from about 4 to 6 containing sufficient thickening agent so that the viscosity is from about 2500 to 6500 cps.
2. A therapeutic composition of Claim 1 wherein the vitamin B₁₂ is cyanocobalamin.
3. A composition as in Claim 1 or 2 additionally containing from about 1% to 10% by weight based on the total weight of a humectant.
4. A composition as in Claim 1 or 2 additionally containing from about 0.2% to 2% by weight based on the total weight of a surfactant.
5. A composition as in Claim 1 or 2 additionally containing from about 1% to 10% by weight based on the total weight of a humectant and from about 0.2% to 2% by weight based on the total weight of a surfactant.
6. A therapeutic composition as in Claim 1 wherein the thickening agent is methyl cellulose.
7. A therapeutic composition of Claim 6 wherein the vitamin B₁₂ is cyanocobalamin.
8. A therapeutic composition of Claim 6 or 7 additionally containing from about 1% to 10% by weight based on the total weight of a humectant and from about 0.2% to 2% by weight based on the total weight of a surfactant.

9. A therapeutic composition for nasal administration in dosage unit form containing from 50 to 1000 micrograms of a vitamin B₁₂ in an isotonic aqueous buffer at a pH of from about 4 to 6 containing sufficient thickening agent so that the viscosity is from about 2500 to 6500 cps.

10. A therapeutic composition as in Claim 9 wherein the vitamin B₁₂ is cyanocobalamin.

11. A therapeutic composition as in Claim 9 or 10 additionally containing from about 1% to 10% by weight based on the total weight of a humectant.

12. A therapeutic composition as in Claim 9 or 10 additionally containing from about 0.2% to 2% by weight based on the total weight of a surfactant.

13. A therapeutic composition as in Claim 9 or 10 additionally containing from about 1% to 10% by weight based on the total weight of a surfactant.

14. A therapeutic composition as in Claim 9 wherein the thickening agent is methyl cellulose.

15. A therapeutic composition as in Claim 14 wherein the vitamin B₁₂ is a cyanocobalamin.

16. A therapeutic composition as in Claim 14 or 15 additionally containing from about 1% to 10% by weight based on the total weight of a humectant and from about 0.2% to 2% by weight based on the total weight of a surfactant.

17. A method of treating a human for vitamin B₁₂ deficiency which comprises nasal administration to a human in need of such treatment a composition containing a therapeutically effective

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amount of a vitamin B₁₂ in an isotonic aqueous buffer at a pH of from about 4 to 6 containing sufficient thickening agent so that the viscosity is from about 2500 to 6500 cps.

18 A method as in Claim 17 wherein the vitamin B₁₂ is cyanocobalamin.

19. A method as in Claim 17 or 18 wherein the composition additionally contains from about 1% to 10% by weight based on the total weight of a humectant.

20. A method as in Claim 17 or 18 wherein the composition additionally contains from about 0.2% to 2% by weight based on the total weight of a surfactant.

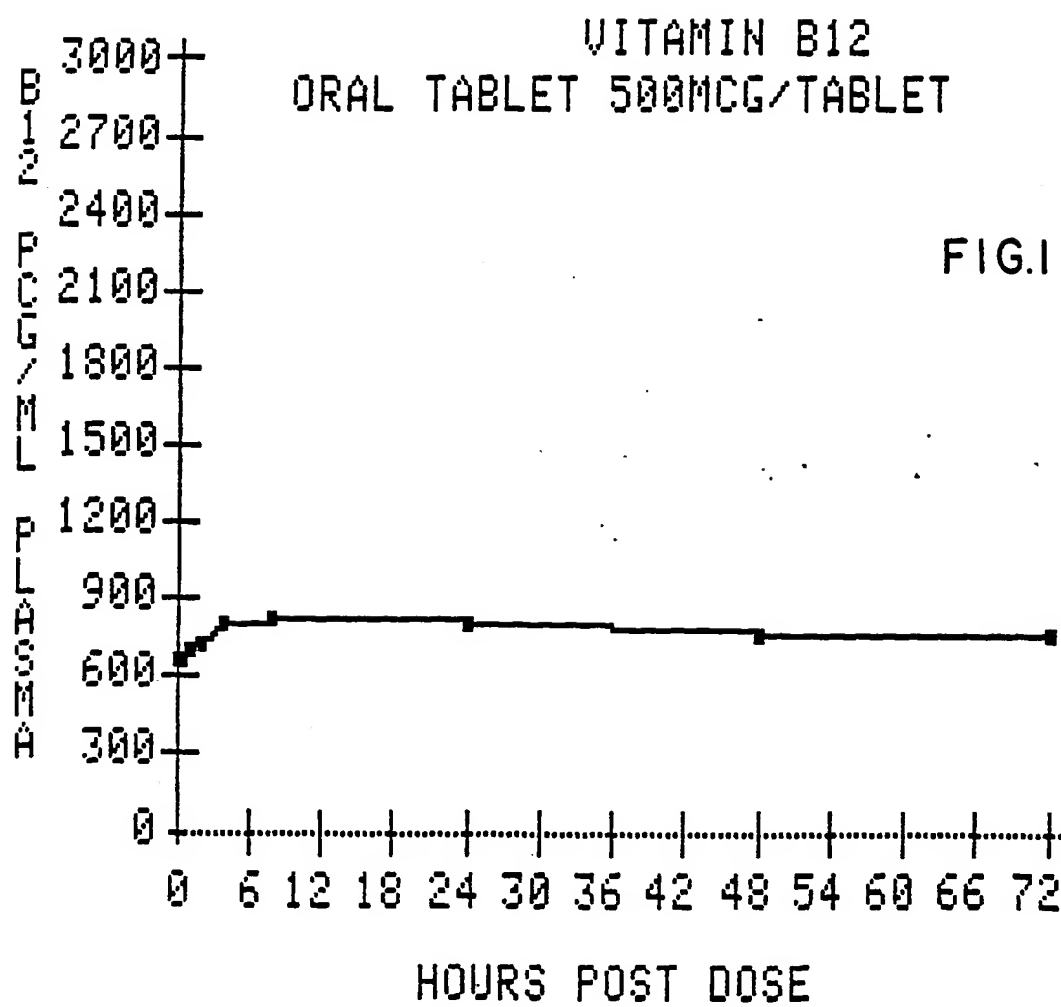
21. A method as in Claim 17 or 18 wherein the composition additionally contains from about 1% to 10% by weight based on the total weight of a humectant and from about 0.2% by weight based on the total weight of a surfactant.

22. A method as in Claim 17 wherein the thickening agent is methyl cellulose.

23. A method as in Claim 22 wherein the vitamin B₁₂ is cyanocobalamin.

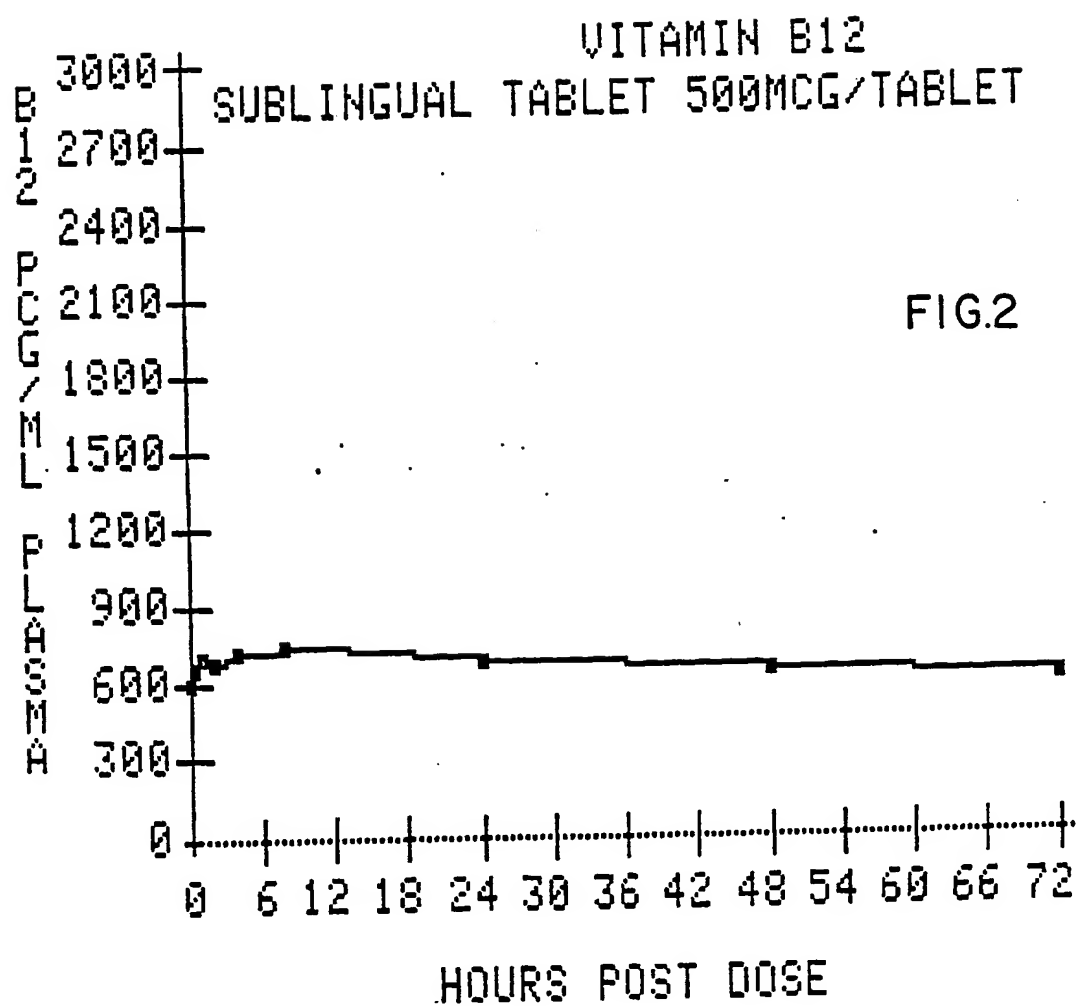
24. A method as in Claim 22 or 23 additionally containing from about 1% to 10% by weight based on the total weight of a humectant and from about 0.2% to 2% by weight based on the total weight of a surfactant.

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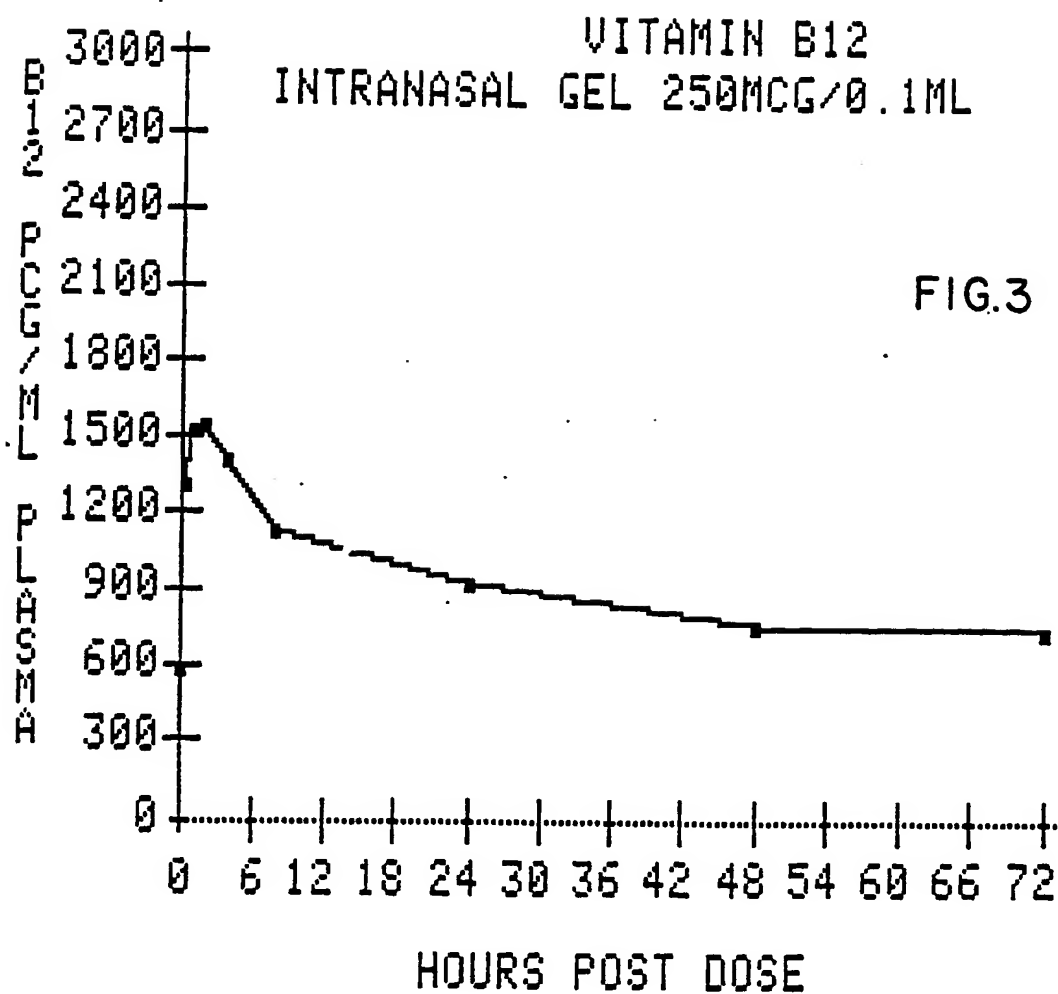
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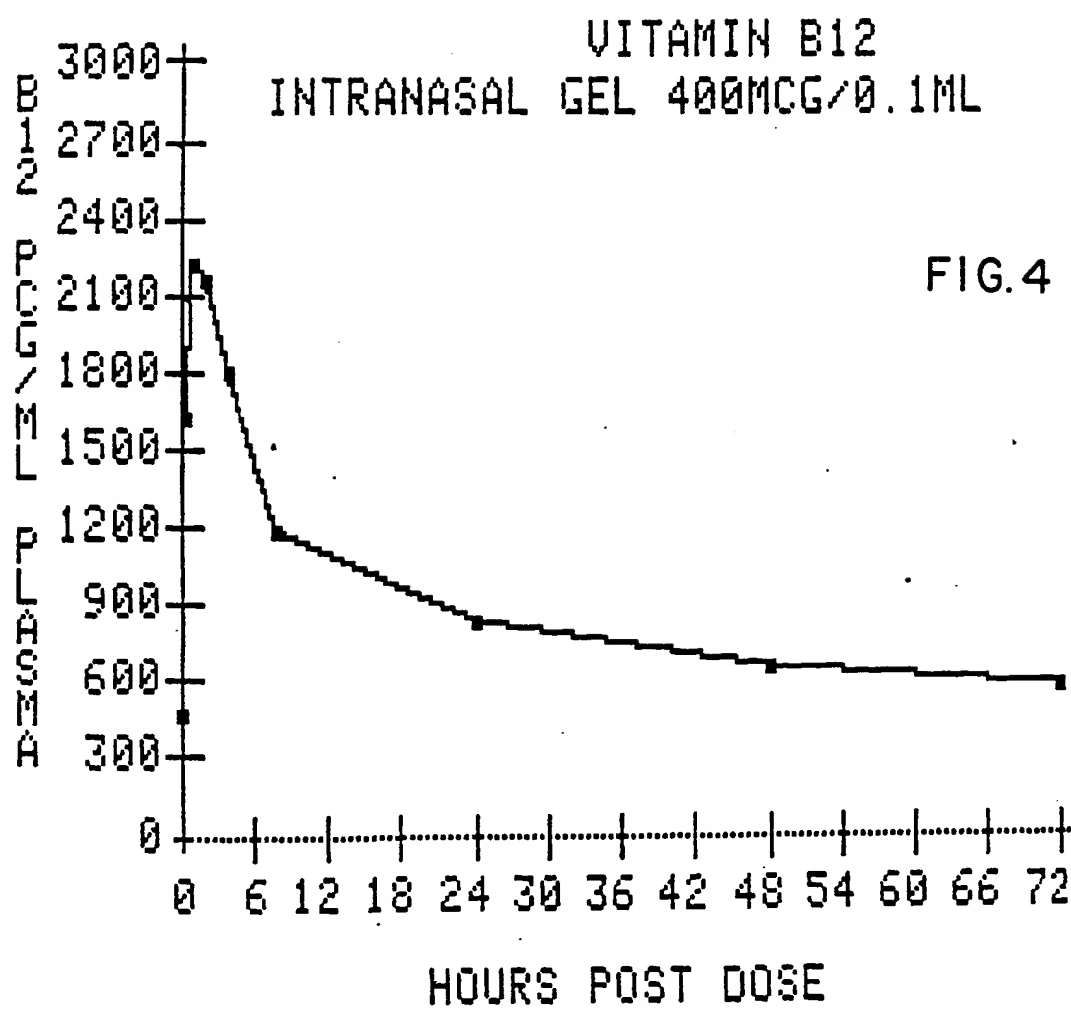


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INTERNATIONAL SEARCH REPORT

International Application No PCT/US86/00793

| | | |
|--|---|-------------------------------------|
| I. CLASSIFICATION OF SUBJECT MATTER (If several classification symbols apply, indicate all) ³ | | |
| According to International Patent Classification (IPC) or to both National Classification and IPC IPC4: A61L 9/04; A61K 31/70 U.S.: 424/45; 514/52 | | |
| II. FIELDS SEARCHED | | |
| Minimum Documentation Searched ⁴ | | |
| Classification System | Classification Symbols | |
| U.S. | 424/45; 514/52 | |
| Documentation Searched other than Minimum Documentation to the Extent that such Documents are Included in the Fields Searched ⁵ | | |
| CAS-ON-LINE: Vitamin B ₁₂ or Cyanocobalamin & Aerosol or Nasal | | |
| III. DOCUMENTS CONSIDERED TO BE RELEVANT ¹⁴ | | |
| Category ⁶ | Citation of Document, ¹⁵ with indication, where appropriate, of the relevant passages ¹⁷ | Relevant to Claim No. ¹⁸ |
| Y | US,A, 4,174,295 (BARGIGIA ET AL.) 13 November 1979, see column 11, lines 12-25. | 1-24 |
| Y,P | US,A, 4,525,341 (DEIHL) 25 June 1985, see the ABSTRACT, column 2, lines 9-12,15-19, 42-47, column 4, Example 1 and column 4 claim 1. | 1-24 |
| X | Chemical Abstracts, Volumn 66, No. 15, issued 10 April, 1967 (Columbus, Ohio, U.S.A). (N.K. SHINTON) "Vitamin B ₁₂ absorption by inhalation" see page 6024, column 2, the abstract No. 64246e. Brit. Med. J. 1967 (5537), 412-413 (Eng). | 1-24 |
| <p>¹⁶ Special categories of cited documents: ¹⁵</p> <p>"A" document defining the general state of the art which is not considered to be of particular relevance</p> <p>"E" earlier document but published on or after the international filing date</p> <p>"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)</p> <p>"O" document referring to an oral disclosure, use, exhibition or other means</p> <p>"P" document published prior to the international filing date but later than the priority date claimed</p> <p>"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention</p> <p>"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step</p> <p>"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.</p> <p>"&" document member of the same patent family</p> | | |
| IV. CERTIFICATION | | |
| Date of the Actual Completion of the International Search ¹ | Date of Mailing of this International Search Report ² | |
| 23 June 1986 | 27 JUN 1986 | |
| International Searching Authority ¹ | Signature of Authorized Officer ²⁰ | |
| ISA/US | Douglas W. Robinson | |

III. DOCUMENTS CONSIDERED TO BE RELEVANT (CONTINUED FROM THE SECOND SHEET)

| Category * | Citation of Document, ¹⁶ with indication, where appropriate, of the relevant passages ¹⁷ | Relevant to Claim No ¹⁸ |
|------------|--|------------------------------------|
| A | U.S., A, 3,282,781 (MACEK ET AL.) 01 November 1966, see entire document. | 1-24 |
| A | U.S., A, 3,584,115 (GEBHART ET AL.) 08 June 1971, see entire document. | 1-24 |
| A | U.S., A, 3,957,966 (VALAN) 18 May 1976, see entire document. | 1-24 |

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